IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Zhu, et al.
Appl. No.	:	10/041,688
Filed	:	January 7, 2002
For	:	ADHESIVE INCLUDING MEDICAMENT
Examiner	:	Ghali, I. A. D.
Group Art Unit	:	1615

DECLARATION OF YONG-HUA ZHU

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Yong-Hua Zhu, declare as follows:

1. I am a citizen of the United States, residing at 1154 W. Highland Avenue, Redlands, California 92373, and believe that I am the original, first and joint inventor with Wolff M. Kirsch, Cindy Dickson, Min Di Gu, Ghang Zheng Yang, and Qun-Dong Shen of the subject matter which is claimed and for which a patent is sought on the invention entitled "ADHESIVE INCLUDING MEDICAMENT"; the specification of which was filed on January 7, 2002 as Application Serial No. 10/041,688.

2. I have read the Office Action dated April 5, 2007, and understand that Claims 1-5, 8, 10-12, 14-17, 20, 23, 24, 26-29, and 31-37 have been rejected under 35 U.S.C. § 103(a) over WO 96/10374 ("WO '374") in view of U.S. Patent No. 6,143,352, ("US '352"); that Claim 22 has been rejected under 35 U.S.C. § 103(a) over WO '374 in view of the '352 Patent, and further in view of WO 96/00760 ("WO '760"); and that Claims 6 and 18 are unpatentable under 35 U.S.C. § 103(a) over WO '374 in view of the '352 Patent, and further in view of WO 99/20685 ("WO '685").

3. In the Examiner's Response to Arguments on Page 7 of the Office Action dated April 5, 2007, it is asserted that the intended use of the capsule as a protective shell to prevent polymerization of cyanoacrylate is obvious and is implied by the teaching of US '352. The

Examiner further asserts "it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a composition and a method for sealing would by applying adhesive composition comprising cyanoacrylate, pore forming agent and antibiotic as disclosed by WO '374, and encapsulated the antibiotics included in the composition in a gelatin capsule as taught by US '353, motivated by the teaching of US '353 that microencapsulation chemically protects the materials that interact with the adhesive and also provides controlled release of the bioactive agents, and one having ordinary skill in the art would have selected gelatin because US '352 disclosed it as a bioerodible material that breakdown in the presence of body fluid, with reasonable expectation of having adhesive wound sealing composition and comprises cyanoacrylate, pore forming agent and antibiotic encapsulated in gelatin capsule to chemically protect the materials that interact with the adhesive and breakdown in body fluid to provide controlled release of the antibiotics, as desired by applicants." I strongly disagree with the Examiner's conclusion.

4. One of ordinary skill in the art would not agree with the broad statement "microencapsulation chemically protects the materials that interact with the adhesive and also provides controlled release of the bioactive agents." To the contrary, one of ordinary skill in the art understands that the microencapsulation efficiency, reflective of the actual amount of therapeutic agent that is encapsulated compared to the theoretical amount of therapeutic agent that could be encapsulated, can vary, e.g., depending upon the microencapsulation technique, the relative proportions of the encapsulant and therapeutic agent, and the process conditions (See, e.g., AAPS PharmSciTech 2003; 4 (3) Article 39 (http://www.pharmscitech.org); Jang-Hyuk Ahn, Young-Pil Kim, Yu-Mi Lee, Eun-Mi Seo, Ki-Woong Lee, Hak-Sung Kim "Optimization of microencapsulation of seed oil by response surface methodology" Food Chemistry xxx (2007) xxx–xxx; Indian J. Pharm. Sci., 2006, 68 (4): 461-464; Acta Pharm. 55 (2005) 57–67; J. Dairy Sci. 84:1576–1582, attached hereto). As the attached literature references demonstrate, microencapsulation efficiency can vary widely, and a high microencapsulation efficiency cannot necessarily be achieved in all situations.

5. Whether or not a low microencapsulation efficiency is acceptable, or instead whether a high microencapsulation efficiency is needed, depends upon the purpose of microencapsulation and the nature of the material to be encapsulated. If the purpose of the microencapsulation is to merely provide for sustained release or delayed release of the

therapeutic agent, then a low microencapsulation efficiency may be acceptable – although a fraction of the therapeutic agent is unencapsulated and immediately available, the fraction of the therapeutic agent that is encapsulated will be released over time according to the microcapsules' release profile. Similarly, if the purpose of microencapsulation is to prevent contact of the therapeutic agent with a substance that destroys or deactivates the therapeutic agent, then a low microencapsulation efficiency may also be acceptable – although the fraction of the therapeutic agent that is unencapsulated will be destroyed or deactivated, the fraction of the therapeutic agent that is encapsulated will be protected from the other substance and thus remain active. On the other hand, if the purpose of microencapsulation is to prevent contact of the therapeutic agent with another substance, because the therapeutic agent has a detrimental effect on the other substance, then a high microencapsulation efficiency may be necessary – the fraction of the therapeutic agent that is not encapsulated will cause the harm that is sought to be prevented, despite the fact that the remaining fraction of the therapeutic agent is encapsulated.

6. As discussed in my previous Declaration, the majority of antibiotics contain active groups which react with cyanoacrylate adhesives. Accordingly, when an antibiotic is directly added to a cyanoacrylate, the antibiotic reacts with the cyanoacrylate such that polymerization occurs and the adhesive immediately solidifies, completely losing its adhesive function. Moreover, the antibiotic that reacts with cyanoacrylate becomes deactivated or exhibits a significant degradation in antibiotic activity.

7. In the adhesives and methods as presently claimed in my and my co-inventor's application, not only is the antibiotic sensitive to deactivation by the cyanoacrylate adhesive, the cyanoacrylate adhesive is sensitive to premature polymerization by the antibiotic. Any unencapsulated antibiotic can potentially cause premature polymerization, hence, a high microencapsulation efficiency is needed.

8. If controlled release of the antibiotic was the sole purpose for microencapsulation, then perhaps it could be argued that there would be some reasonable expectation of success in applying the methods of US '352 in microencapsulating antibiotics, as a low microencapsulation efficiency might be tolerated provided that at least some antibiotic was encapsulated. However, there can be no reasonable expectation of success if a high microencapsulation efficiency is needed. US '352 includes no teaching as to microencapsulation efficiency of the disclosed method and materials, much less specific information as to how to provide a high

microencapsulation efficiency for an antibiotic instead of the disclosed pH modifiers, or using a gelatin encapsulant rather than the polymers of the examples. Because microencapsulation efficiency varies so widely dependent upon the encapsulant, the material to be encapsulated, the process conditions, and the microencapsulation technique (see attached technical articles), there can be no reasonable expectation of success in applying the methods of US '352 to prepare microcapsules with a protective shell around an antibiotic to prevent premature polymerization of the cyanoacrylate by blocking direct contact between the antibiotic and the cyanoacrylate.

9. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 10/8/07

Yong-Hua Zhu

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